Review
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Optimizing Abiraterone Delivery through Intratumoral In Situ Implant: A Prospective Pharmaceutical Development Approach

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Abstract: Abiraterone acetate is one of the effective therapies in castration-resistant prostate cancer. There is only one dosage form in the form of film-coated tablets. Abiraterone has proven effective but has disadvantages and contraindications that complicate therapy. One of them is a positive food effect affecting the bioavailability and side effects of the drug. Abiraterone is taken strictly on an empty stomach, and the bioavailability of the drug, in this case, reaches only 10%. In addition, the drug is contraindicated in people with hepatic insufficiency since the main metabolism is in the liver. These and other disadvantages can be eliminated by obtaining targeted delivery systems - liposomes and nanocrystals. Another dosage form could be considered for the active pharmaceutical agent that would be cost-effective, accessible and have higher bioavailability for effective treatment. An intratumoral polymeric in situ implant is chosen as an excellent dosage form, the matrix of which will contain an optimized form of abiraterone, which can stably target a tumor.

Introduction

Prostate cancer (PC) is the second most common cancer globally, affecting men of all racial and ethnic groups. PC leads to high mortality among most middle-aged and older men from 45 to 60 years due to late diagnosis among people belonging to a low social class and ineffective treatment (1). In addition, besides social and environmental influence, there is a genetic influence leading to gene mutations. Long-term studies confirm that one of the genetic risk factors is heredity, which reduces the chances of survival (2). To date, there is no single specific test for prostate cancer. It is traditionally diagnosed using a rectal examination, transrectal ultrasound (TRUS), prostate-specific antigen (PSA) test, and a prostate needle biopsy.

If the tumor is localized, PC treatment includes stereotactic radiotherapy, radical prostatectomy, and active surveillance. In most cases, after chemical or surgical castration, patients experience recurrence or metastatic castration-resistant prostate cancer (mCRPC) treated with androgen deprivation therapy (ADT), radiation therapy, or chemotherapy. Each listed treatment method is costly, energy-consuming, has serious side effects, toxic, resistance to treatment, and is a prerequisite for developing concomitant diseases (3). Therefore, we should find a cost-effective and effective drug in the most convenient dosage form that allows high bioavailability for the maximum therapeutic effect and is effective in combination with other drugs, regardless of the stage and metastasis of PC. Based on the previous report, abiraterone is chosen as the active pharmaceutical ingredient (API), which has proven to be a very effective first-line drug for mCRPC.

Abiraterone acetate, a prodrug of abiraterone, is a selective and irreversible antagonist of the cytochrome P450 (CYP17) enzyme, which plays a key role in androgen biosynthesis in testes, adrenal glands, and prostate tumor cells. Further use of abiraterone results in virtually undetectable serum and intratumor androgen levels. Abiraterone acetate is combined with low doses of prednisolone to overcome side effects since inhibition of CYP17 reduces the production of endogenous glucocorticoids. Abiraterone acetate

rapidly hydrolyzes to abiraterone and reaches its maximum plasma concentration within two hours. However, the absolute bioavailability of the drug is still not studied due to its low solubility and permeability (4). Abiraterone acetate is taken orally in tablet form on an empty stomach. The rationale for this recommendation is that the drug's bioavailability is influenced by the amount of dietary fat ingested, which can substantially impact the drug's efficacy (5). In addition to low bioavailability, abiraterone is contraindicated with severe hepatic insufficiency since the drug is metabolized mainly in the liver, which leads to reduced drug elimination and increased levels of aspartate transaminase (AST), alanine transaminase (ALT) and bilirubin in the blood test (6). Despite the disadvantages, the drug has a proven efficacy in an inverse relationship: an increase in the concentration of abiraterone and a decrease in prostate-specific antigen (PSA). Also, an increase in survival, the average life expectancy, and the overall quality of PC patients occur (7).

There have been previous attempts to increase the bioavailability of abiraterone. For example, the concept of the formulation of oil balls with a dissolved drug was developed, where it was proved to increase the bioavailability of abiraterone by 2.7 times in AUC and 4.0 times in Cmax (8). It is also worthwhile to mention the experience of developing a lipid-based formula for abiraterone acetate using a supersaturated silica and lipid hybrid (super-SLH) approach to achieve high drug loading (9). As a result, a higher level of solubilization was achieved compared to Zytiga. And in a study by Urvi Gala et al. (10) with the help of KinetiSol technology, they were engaged in the formation of a solid amorphous dispersion of abiraterone. At the end of the trial, the potential to eliminate the food effect and increase the solubility of abiraterone was found. Despite the above examples, the issue of bioavailability, cost-effectiveness, and production rate of a bioavailable API is still open.

Thus, this review aims to substantiate the need and prospects for developing a new effective targeted delivery system for chemotherapy using abiraterone - an intratumoral in situ system.

Main Part

PC is an androgen-dependent malignant neoplasm. First, it was demonstrated in 1941 in Huggins and Hodges's research, which showed that lowering serum androgen levels by orchiectomy or administration of exogenous oestrogen caused tumor regression and symptomatic relief (11). Huggins and Hodges were awarded the Nobel Prize for this research. Drugs that block androgen synthesis were used as first-line therapy (12). As the primary treatment, androgen deprivation is usually achieved by orchidectomy or luteinizing hormone-releasing hormone (LHRH) analogs, often combined with androgen receptor antagonists to block residual adrenal androgens. However, a problem remains unresolved, and almost all patients eventually relapse (13). Second-line treatment included alternative endocrine manipulations and chemotherapy.

Therefore, when it became relevant to the use of P450 inhibitors, it was found to provide maximum ablation of androgens after a single use, blocking their synthesis in the testicles and adrenal glands. High-dose ketoconazole was used, but not widely due to severe side effects. Medical adrenalectomy (aminoglutethimide + hydrocortisone) has become obsolete by generalizing maximum androgen blockade in first-line treatment (14).

In reviewing articles related to the development and research of abiraterone acetate, the PubMed database was analyzed from 1994 with a research of the cytochrome P450 steroid inhibitors pharmacology (15). According to the previous works, the search for an effective CYP17 inhibitor dates back to the 60s of the last century (16). But since the 90s, work has begun researching the abiraterone acetate effectiveness and its application (17). The molecule was first discovered in 1990 at a research center in London by Dr. Jerry Potter (18).

Gerhardt Attard et al. reviewed a Phase I clinical trial of abiraterone acetate in chemo-naive men with prostate cancer resistant to multiple hormonal therapies (19). Patients took the drug up to 5 doses at a time (from 250 to 2000 mg), and it was found that abiraterone acetate is tolerated very well. Antitumor activity was observed at all doses. Since CYP17 catalyzes the last step in androgen biosynthesis, target inhibition should affect the production of androgens by the testes and the adrenal glands. Therefore, abiraterone acetate has advantages over existing therapies, such as LHRH analogs.

Phase II research has indicated a significant decrease in PSA levels among castration-resistant patients treated with abiraterone before and after cytotoxic chemotherapy. And in phase III, the drug proved to be quite promising in randomized trials in patients with progression of mCRPC during docetaxel-based chemotherapy (20).

Problems of Low Bioavailability

According to the biopharmaceutical classification system (BCS) (21), abiraterone belongs to class IV drugs and has many characteristics that are problematic for effective oral administration. These include low solubility, low solubilization, and unstable food bioavailability. The latter is the subject of a study by Marlies Braeckmans et al. (22), who explored the

positive food effect of oral abiraterone acetate (commercial name "Zytiga", approved by the Food and Drug Administration (FDA) in 2011). The prodrug is an ester of the abiraterone active compound and is a prime example of a highly lipophilic drug that dissolves better in human intestinal fluids after meals. Despite this, the prodrug should be taken on an empty stomach to avoid side effects of unstable bioavailability (23). Due to limited absorption on an empty stomach, the dose is 1000 mg daily, mainly excreted in the feces (24). In the experiment for this study was using the intact intestinal barrier, which is present in the in situ perfusion method in rats with mesenteric and blood sampling. After evaluating satiety imitation in vitro, lipids and cleaved lipid products increased abiraterone acetate solubility but limited abiraterone permeability. Then these processes were combined into an in situ perfusion model in rats. At a static state of satiety, the concentration of abiraterone in the perfusate was very high, contributing to active absorption. But during digestion, an increased flow of abiraterone was observed compared to fasting, despite its low concentration in the perfusate (22). Thus, at the moment, the mechanisms of the positive food effect are not elucidated. And the question is still open where additional studies are required to evaluate lipid digestion and its impact on abiraterone.

Solution

Despite the problem of positive food effects, several technologies have recently been developed to increase the solubility and bioavailability of drugs that do not have these functions. Solid lipid nanoparticles (SLNs) based on beeswax and theobroma oil in a 1:1 ratio are one example, which remain in a solid state upon drug release and effectively prevent premature leakage (25). These technologies also include polymer micelles, which are a means for dissolving insoluble or poorly soluble chemical compounds and loading the drug exceeding its mass (26). The oral bioavailability improvement is addressed by modeling absorption based on in vitro dissolution measurements, mathematically predicting dose-absorbed fractions in different biorelevant media (27). Orsolya Basa-Dénes et al. developed a nano amorphous formulation of abiraterone acetate by enzymatic hydrolysis that demonstrated higher obvious solubility and dissolution rate, and significantly improved absorption and fasting bioavailability in beagle dogs, significantly altering the pharmacokinetics of the drug (28). Also, continuous flow precipitation technology obtained the new form of abiraterone acetate. It allows the compound to be rapidly absorbed and predicts that a dose of 250mg of the new drug will give the same exposure as 1000 mg Zytiga in the fasted state. Thus, the toxic effect is reduced (29). Other work presented a rational approach to developing new drug formulations to increase fasting bioavailability. As in the previous example, precipitation experiments were performed in biorelevant media to evaluate drug precipitation. Two main approaches areused to form the new abiraterone. The first approach is to suppress precipitation from a supersaturated solution. At the same time, the second is based on the hypothesis that adjusting the drug's release can achieve its optimal absorption. Both approaches increase the fasting bioavailability of abiraterone acetate, with up to 250% increased bioavailability in experimental animals compared to the parent drug having a crystal lattice structure (30). In the following article, Hayley B Schultz et al. investigated the efficacy of silica-lipid hybrids (CLG) and supersaturated silica-lipid hybrids (pCLG), where CLG showed a 1.43-fold improvement in the oral bioavailability of abiraterone acetate (31).

In 2021 research, cyclodextrin complexes were developed to encapsulate the drug and improve solubility using the example of gold compounds, which almost completely retained their biological activity when creating the complex (32). These studies were continued with citrate-mediated synthesized gold nanoparticles with immobilized surrogate antibodies that were bioconjugated into the substantially potent drug abiraterone for development as a combinatorial therapeutic agent against prostate cancer (33). However, Yuanfen Liu et al. (34) created nanocrystalline tablets of abiraterone acetate, which increased oral bioavailability. This dosage form is obtained by the dry granulation method, where freeze-dried nanocrystals, fillers, stabilizers, and disintegrants are precisely weighed, mixed, and then compressed into flakes. The formula has been optimized and stable. As a result, the rate of abiraterone acetate nanocrystal tablets is similar to the Zytiga reference tablet in vitro, while the in vivo oral bioavailability is increased by 2.8 times, indicating that the nanocrystals can effectively improve the oral absorption of insoluble drugs. It is also interesting to study the synthesis of a low molecular weight abiraterone conjugate targeting the prostate-specific antigen membrane. The conjugate showed a preferential effect on prostate tumor cells, reducing prostate-specific membrane antigen expression and showing significantly reduced acute toxicity with comparable efficacy compared to abiraterone acetate (35).

Nanocrystals, or nanosuspensions, are semi-crystalline structures with an API and surrounding stabilizers (36). The drug shows absolute safety and stability if the excipients are used in small quantities. Then it is also suitable for injection and inhalation procedures (37). API dissolved in nanocrystals can be absorbed in the molecular state due to passive or transcellular transport reaching the bloodstream (38). These facts suggest that nanocrystals can be used for in situ implant dosage form, although the problems of stabilization and prolongation should still be solved.

In Situ Systems as a Solution of Classical Intratumoral Implants in Modern Chemotherapy

Compared with intravenous or oral administration, direct intratumoral in situ drug delivery reduces systemic absorption, general side effects, and increased chemotherapy toxicity and targets the API directly to the tumor (39). Classical implants are biodegradable polymers of various structures implanted directly inside the tumor (for example, needle type) or located directly around it (40). There are also intratumoral injections, the introduction of which is associated with less traumatic manipulation (41).

However, unlike the implant, injections do not have a prolongation, are more toxic, and the high pressure of the interstitial fluid of the tumor prevents the drug from being delayed at the injection site. Modern targeted delivery systems (in situ systems) change their states of matter due to a phase transition at the injection site. They can become a compromise that combines the effectiveness of classical implants and the convenience of injections (42). The formation of an in situ implant occurs due to the tumor's pathological factors, the injection site's physiological characteristics, or exposure from outside - irradiation or heating of the implantation site (43).

To date, a commercially available drug for intratumoral implantation is GLIADEL® Wafer, a biodegradable implant designed for treating brain cancer (44). This innovative implantation method entails surgical intervention, as it involves the precise placement of the wafer at the site where the tumor has been surgically removed, thereby facilitating targeted treatment and reducing the risk of cancer recurrence. However, despite its effectiveness, this procedure is not without risks, as its invasiveness may lead to potential complications such as pain, bleeding, or infection if the desired outcomes are not achieved.

Considering this issue, Changkyu Lee (45) developed a starch-based needle implant with high rigidity, injected or using an endoscope in case of difficult tumor access. Starch is an inexpensive, readily available, and biodegradable biopolymer. When heated, the crystal lattice structure is destroyed, and the starch acquires a gel-like structure (46, 47). Such a texture easily acquires the required shape and size, and the API is encapsulated (for example, stabilized nanocrystals of the active substance can be considered). The starch recrystallizes and becomes ready for use. Since the industrial production of starch implants is very economical and easily reproducible, it can be assumed that this method can become a new strategy for treating cancerous tumors.

Perspective on the Development of the In Situ Implant of Abiraterone Acetate

The low levels of solubility and absorption of abiraterone, characteristic of the BCS class 4 API, limit the possibilities of using this API in situ systems. The first step in the pharmaceutical development of a new delivery system for abiraterone will be the selection of an appropriate solvent or optimal solubilization process. The choice of the stimulating factor and the composition of the system matrix will depend on the chosen method (48). For example, using thermosensitive matrices based on poloxamers can give unsatisfactory results for abiraterone acetate since poloxamers often cannot solubilize BCS class 2 and 4 APIs (49). Simultaneously, the creation of systems such as solid dispersions that can solve the problem of abiraterone acetate solubility may also not give positive results due to the aggregative instability of the complex (50). Thus, phase-sensitive matrices in which the API is dissolved in a suitable indifferent non-aqueous solvent (NMP, etc.) diffuse into the surrounding soft tissues after injection can be identified as promising in situ systems for the delivery of abiraterone.

Conclusion

Intratumoral implantation with abiraterone can become an adequate replacement for the oral dosage form. Its advantages include optimized API, prolongation, high targeting, good tolerability, and no systemic effects. It can positively affect the quality of life of people taking this drug. In addition, the implant can be widely used due to the choice of cost-effective and affordable means of production. Despite the current problem of the stability and bioavailability of abiraterone, there are great chances for a positive trend for treating PC.

Declarations

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Conflict of Interest
The authors declare no conflicting interest.

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